REMARKS

Claims 38-85 are pending in this application. Claims 38-85 have been examined and stand rejected. A Notice of Appeal was filed on June 10, 2005. Prosecution was reopened by the Examiner and a non-final Office Action was mailed on March 7, 2006. Claim 69 has been amended. Reconsideration and allowance of Claims 38-85 is respectfully requested.

The Claim of Priority

The Examiner has noted applicants' claim for priority to US Patent Application No. 09/294,453, filed 4/19/99; which is a continuation of U.S. Patent Application No. 08/986,650, filed 12/8/97, now Patent No. 6,326,140; which is a continuation of U.S. Patent Application No. 08/512,753, filed 8/9/95, now Patent No. 5,777,888. However, the Examiner has taken the position that the instant application is not entitled to the benefit of prior filed Application Nos. 09/294453, 08/986650 and 08/512753 because in the Examiner's view, the disclosure of the prior filed applications fails to provide adequate support for a matrix of probes comprising a predetermined sequence of nucleotides that are hybridizable to genes, transcripts of genes or cDNA. Applicants wish to point out that the specification of the instant application is identical to Application Nos. 09/294453, 08/986650 and 08/512753. Therefore, for the reasons described below in connection with the rejection of Claims 38-85 under 35 U.S.C. § 112, first paragraph (written description), it is submitted that the instant application is entitled to the benefit of the priority claim to August 8, 1995.

The Objection to the Specification

As requested by the Examiner, the specification has been amended to correct the citation for Fodor et al. (1991) *Science 251*, 767-773 and to include material incorporated by reference from Fodor et al., 1991 describing an example of a method for making an array of oligonucleotides having predetermined sequences on a silicon substrate. The material being inserted is the material previously incorporated by reference into the instant application. No new

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matter has been added in compliance with 37 C.F.R. 1.57(f). A copy of Fodor et al. (1991) *Science 51*, 767-773 is attached hereto as Attachment A. Applicants wish to point out that portions of Fodor et al. (1991) that are not explicity included in the amendment to the specification submitted herewith are still considered to be incorporated by reference in the instant application.

The Rejection of Claim 69 Under 35 U.S.C. § 101

Claim 69 stands rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter. The Examiner has taken the position that data in computer readable memory is not patentable subject matter. In particular, the Examiner notes that the claimed data does not affect how the computer processes the data.

Claim 69 has been amended to clarify the claimed invention and now recites "[a] computer memory storing an output signal data structure database produced by the method of claim 56, said output signal data structure database comprising a plurality of stored digital signals, wherein each stored digital signal is associated with (i) a stimulus and (ii) with the identity of an identified gene." Applicants wish to point out that Claim 69 as amended is directed to functional descriptive material consisting of a data structure which imparts functionality when employed as a computer component. The definition of "data structure" is a "physical or logical relationship among data elements, designed to support specific data manipulation functions." *See* MPEP § 2106(IV)(B)(1). As stated in the MPEP, "[w]hen functional descriptive material is recorded on some computer readable medium (e.g., a computer memory) it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized." MPEP § 2106(IV)(B)(1), citing *In re Lowry*, 32 U.S.P.Q.2d 1031, 1035 (Fed. Cir. 1994).

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Accordingly, for at least the foregoing reasons, applicants request removal of this ground of rejection.

The Rejection of Claims 38-85 Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 38-85 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner has taken the view that the specification does not describe a matrix of probes comprising a predetermined sequence of nucleotides, or how to make such a matrix. Applicants disagree for the following reasons.

It is submitted that the specification provides adequate written description support for the claimed invention in view of the knowledge in the art at the time of the earliest priority filing. As stated in the PTO Guidelines, 66 Fed. Reg. at 1106, the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics which coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *See also Enzo Biochem. Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002) (stating that written description requirement may be met by disclosure of functional characteristics when coupled with a known or disclosed correlation between function and structure.). Furthermore, the Federal circuit has recently held that when the prior art includes the relevant sequence information, there is no *per se* requirement that the specification needs to include the sequence. (*Capon v. Eshhar*, 418 F.3d 1349 (Fed Cir 2005).

The Examiner has taken the view that the specification makes no mention of a matrix with predetermined sequences. Applicants disagree. Contrary to the Examiner's assertion, the specification provides numerous examples of a matrix with identified genes having predetermined sequences. As an example of a genome reporter matrix with predetermined

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sequences, the specification describes: "[t]o generate a genome reporter matrix 610 a set of lacZ fusions are constructed to a comprehensive set of yeast genes. The fusions are generally constructed in a diploid cell of the a/a mating type to allow the introduction of dominant mutations by mating, though haploid strains also find use with particularly sensitive reporters for certain functions. The fusions are arrayed onto a grid separating distinct fusions into units having defined X-Y coordinates. The *gene identification function* 612 is performed by *determining, for each reporter-tagged gene, a short sequence adjacent to the site of fusion. That sequence is then compared with the yeast genomic database to establish the identity of the gene. An index table 614 is established relating each gene in the matrix to the X-Y coordinate of the fusion construct for that gene.*" Specification at page 14, lines 24-32, emphasis added.

As another example, the specification at page 3, lines 10-13 states "the arrays may comprise the organism's entire repertoire of responders which may be *genes, gene regulatory elements, gene transcripts or gene translates*, or a *predetermined functional class or subset of the organism's entire repertoire.*" Other examples of support in the specification for a matrix with predetermined sequences include page 8, lines 31 to page 9, line 1: "[b]*y knowing the identity of the gene* being reported in each strain, the genome-wide response is interpreted." At page 9, lines 13-18 the specification states: "a genome reporter matrix reveals the spectrum of other genes in the genome also affect by the compound... Because *the identities of the reporters are known* or determinable, information on other affected reporters is informative as to the nature of the side effect." Another example of support for predetermined sequences is found in the specification on page 11, line 20-21: "*the identity of that gene* provides a guide to the target of the new compound."

The specification also provides detailed guidance on how to make a matrix with predetermined sequences, for example as described on page 18, lines 15-18: "unlabeled *oligonucleotide hybridization probes complemetary to the mRNA transcript of each yeast gene*

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are arrayed on a silicon substrate etched by standard techniques (e.g. Fodor et al. (1991) *Science 251*, 767). The probes are of length and sequence to ensure specificity for the corresponding yeast gene, typically about 24-240 nucleotides in length." (*See* Specification page 18, lines 15-18). The specification has been amended as described above, to include the description in Fodor et al. 1991 that was incorporated by reference.

At the time of invention, a multitude of gene sequences were publically available that were useful to practice the method of the invention. For example, as described in the specification, it was known that the total number of genes in Saccharomyces cerevisiae was approximately 6,000. (*See* Specification at page 8, lines 19-21). Applicants wish to point out that in 1995, 70% of yeast sequences were publically available as a result of a yeast genome project. Exemplary journal articles are filed herewith that relate to knowledge of skill in the art regarding the yeast genome project. For example, *see* Johnston et al., *Science 265* (5181): 2077-82 (1994), attached hereto as Attachment B; Bussey et al., *PNAS 92*: 3809-3813 (1995), attached hereto as Attachment C; Murakami et al., *Nature Genetics 10(3)*: 261-8 (1995), attached hereto as Attachment D; Dujon, B. *Trends in Genetics 12(7)* (1996), attached hereto as Attachment E; and Hieter et al., *Nature Genetics 13*: 253-255 (1996), attached hereto as Attachment F. Moreover, the invention disclosed and claimed is not limited to any particular target organism. At the priority date of the application there were active genome projects for many organisms, including Drosophila melanogaster, E. coli, B. subtilis, C elegans and Homo sapiens. Accordingly, as of the earliest priority date of August 9, 1995, a skilled worker was able to practice the invention.

Therefore, it is submitted that the written description requirement of pending Claims 38-85 is met in view of the disclosure in the specification coupled with the knowledge in the art. As described *supra*, the nucleic acid sequence of the majority of yeast genes were known

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in the art and therefore one of skill in the art would have possession of this information at the time of filing. Therefore, applicants respectfully request withdrawal of this ground of rejection.

The Rejection of Claims 38-53, 55-66, 68-83 and 85 Under 35 U.S.C. § 102(a) or Under 35 U.S.C. § 102(e) in view of Fodor et al., 2001 (US Patent No. 6,309,822)

For at least the reasons submitted in response to the rejection of Claims 38-85 under 35 U.S.C. § 112, first paragraph (written description) it is submitted that the instant application is entitled to the benefit of the priority claim to August 8, 1995. Therefore, it is submitted that Fodor et al., 2001 (US Patent No. 6,309,822) is not citable as prior art to the instant application. Applicants respectfully request removal of this ground of rejection.

The Rejection of Claims 38-53, 55-66, 68-83 and 85 Under 35 U.S.C. § 103(a) As Being Unpatentable Over Gress et al., in view of Granelli-Piperno et al. in view of either Fodor et al. 1998 (US Patent No. 5,800,992) or Fodor et al., 1991

Claims 38-53, 55-66, 68-83 and 85 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gress et al. in view of Granelli-Piperno et al. in view of either Fodor et al. '98 (US Patent No. 5,800,992) or Fodor et al. '91.

As an initial matter, for at least the reasons submitted in response to the rejection of Claims 38-85 under 35 U.S.C. § 112, first paragraph (written description), it is submitted that the instant application is entitled to the benefit of the priority claim to August 8, 1995. Therefore, it is submitted that Fodor et al., 2001 (US Patent No. 6,309,822) is not citable as prior art to the instant application.

The Examiner has taken the view that Gress et al. discloses a method of assaying patterns of transcription by use of labeled cDNA from mouse and human cells by the use of a cDNA X-Y coordinate grid array of probes. Gress et al. is further cited as disclosing the importation of resulting data via an electrical signal of a Phosphorimager to a computer implemented relational database. The Examiner acknowledges that Gress et al. does not show subjection of assayed

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cells to different stimuli, or comparison of the transcriptional profile of cells that have received different stimuli or use of probes with a predetermined sequence of nucleotides. The Examiner has taken the view that Granelli-Piperno et al. discloses that assay of expression of genes after treatment of cells with drugs allows a determination of the effect of the drug on individual gene expression via intensity of a film image on an autoradiograph. Fodor et al. '91 is cited by the Examiner as disclosing a method of synthesizing a dinucleotide of a predetermined sequence by a photolithographic process. The Examiner then concludes that it would have been obvious to a person of ordinary skill to modify the method of Gress et al. by assaying cells that have received treatments with different drugs according to the method of Granelli-Piperno et al. The Examiner further concludes it would have been obvious to make and use an array of probes with a predetermined sequence as disclosed by Fodor et al. '91.

It is submitted that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the referenced teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); Manual of Patent Examining Procedure (M.P.E.P.) (8th Ed. Aug. 2001, rev. May 2004) Sections 706.02(j), 2142 and 2143. As stated in *In re Fritch*, 972, F.2d 1260, 1266, 23 USPQ2d 1780, 1784, (Fed. Cir. 1992), it is impermissible to use the claimed invention as an instruction manual or "template" in attempting to piece together isolated disclosures of the prior art so that the claimed invention is rendered obvious.

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It is submitted that the Gress et al. reference, when read in its entirety, actually teaches away from the claimed invention. Gress et al. discloses a method of hybridization fingerprinting analysis involving labeling total cDNA pools derived from different tissues and hybridizing the labeled cDNA pools to cDNA library arrays to *identify* clones in the cDNA library containing mRNA sequences expressed at *middle to high abundance* (Gress et al. at page 609, second column). The goal of the approach described in Gress was to allow the characterization of large numbers of cDNA library clones with a minimal number of experiments (page 609, first column). As stated in Gress the system was used to analyze "clones *abundantly expressed* in several tissues that most likely code for proteins involved in structural and regulatory functions in every cell." (Page 610, first column). Therefore, it appears that the methods of Gress et al. is not suitable for the detection of low abundance transcripts in a cDNA library, thus it would not be suitable for measuring differences in gene expression. Moreover, as noted by the Examiner, Gress shows that polyA control probes hybridize non-specifically to many array cDNA probes and that other cDNA probes in the array contained repetitive sequences that also caused non-specific hybridization. As stated in Gress, "[a] polyA-homopolymer probe hybridized to a considerable number of clones identified with cDNA pools (30-40% for HFB and 7-12% for Drosophila; Table 1, Figs 1b and 3e)." As further stated in Gress et al., "a control hybridization with a PolyA homopolymer proved *essential*, as up to 45% of identified clones may appear positive by hybridization of labeled PolyA tails to large stretches of PolyT in the cloned cDNA." (Gress et al. at page 615-616, emphasis added). In addition, Gress et al. states "[c]ontrol hybridization with total genomic DNA allowed the detection of additional clones positive owing to hybridization with other labeled repetitive sequences in the pool probe. An efficient elimination of all 'false positives' is possible only with the strategy presented here. Other groups have encountered the same problems and have tried to reduce them by different competition techniques (Dworkin ad Dawid 1980, Crampton et al. 1980). *Our experiments demonstrate that*

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even a maximal competition with PolyA/PolyU-homopolymers and genomic DNA is not sufficient to eliminate these background problems completely." (Gress et al. at page 616, first column, emphasis added).

Moreover, with regard to the computerized image analysis, as further described in Gress et al., "[m]uch time and effort was invested in this part of the approach; in particular, the standardization and optimization of the image analysis system proved demanding. A large scale of grey values is generated in one single-tissue cDNA pool hybridization, and the determination of adequate grey value thresholds allowing one to distinguish between "positives and negatives" in each individual experiment is not a simple matter." (Gress et al. at page 616, second column). Also mentioned in Gress et al. is "the difficulty in comparing results with previous experiments (controls and hybridization fingerprints)." (Gress et al. page 617, second column.). Accordingly, it is submitted that the teachings of Gress et al. describe the difficulty of obtaining reliable and reproducible gene expression data from the type of hybridization array described in Gress et al. (i.e. a cDNA library spotted in a 96 well plate). Moreover, the method of Gress et al. is described as being useful for detecting expression of genes abundantly expressed, and therefore would not motivate one to use the methods of Gress et al. to measure relative levels of gene expression.

The Examiner acknowledges that Gress et al. does not teach or suggest subjection of assayed cells to different stimuli or comparison of the transcriptional profile of cells that have received different stimuli. It is submitted that Gress et al. actually teaches away from the claimed invention because the teachings of Gress et al. would not provide any expectation of success that would motivate one to modify the teachings of the Gress et al. reference or any other cited reference to analyze the effects of subjecting a living thing to a stimulus comprising detecting physical signals from a plurality of units ordered in a probe matrix. *See* MPEP 2144.08, *In re Vaeck*, 947 F.2d at 493. (A proper obviousness analysis requires consideration of

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"whether the prior art would have revealed that in so making or carrying out the claimed invention, those of ordinary skill would have a reasonable expectation of success.")

The Examiner also acknowledges that Gress et al. is silent with respect to the use of predetermined sequences. Moreover, applicants wish to point out there is no teaching or suggestion in Gress et al. to store in digital form an electric output signal in an output signal data structure, wherein each stored digital signal is associated: "(i) with said stimulus and (ii) with the identity of the identified gene" as required by the claimed invention.

The Examiner cites Granelli-Piperno et al. as disclosing that assay of expression of genes after treatment of cells with drugs allows a determination of the effect of the drug on individual gene expression and further serves to gain insights on the mechanism of action of the drug. It is submitted that the teachings of Granelli-Piperno et al. do not cure the deficiencies of Gress et al. Granelli-Piperno et al. describes Northern blot analysis of nine lymphokine mRNAs known to be involved in T cell stimulation in order to compare expression of the lymphokine mRNA expression in terms of kinetics, mitogen requirements, and sensitivity to cyclosporin A. Granelli-Piperno et al. does not teach a plurality of units ordered in a probe matrix, wherein each unit of the plurality of units confines a probe comprising a pre-determined sequence. Rather, the methods described in Granelli-Piperno et al. relate to the use of a nitrocellulose filter containing total cellular RNA isolated from T cells that is hybridized with individual probes specific to nine genes known to be involved in T cell stimulation (*see* Granelli-Piperno et al., page 923, third paragraph). Moreover, there is no teaching or suggestion in Granelli-Piperno et al. to store in digital form an electric output signal in an output signal data structure, wherein each stored digital signal is associated: "(i) with said stimulus and (ii) with the identity of the identified gene" as required by the claimed invention.

The Examiner cites Fodor et al., '91 as teaching a method of synthesizing a dinucleotide of a predetermined sequence by a photolithographic process. It is submitted that the teaching of

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Fodor et al., '91 do not cure the deficiencies of the cited references. As previously submitted by the Applicants in the Appeal Brief filed on July 19, 2005, the modification of the method of arraying unidentified cDNA clones that are arrayed on a nitrocellulose filed, or other substrate, as taught by Gress et al., with oligonucleotides having known sequences, as taught by Fodor et al., '91, would render the Gress et al. invention inoperable for its intended purpose of identifying previously unidentified cDNA clones with moderate to high levels of expression.

Moreover, there is no motivation to combine the teachings of Gress et al. with Fodor et al. As described above, it is submitted that the teachings of Gress et al. teach away from the present invention and therefore one of skill in the art would not be motivation to modify the method of characterizing cDNA library clones as taught in Gress with an array of probes as taught in Fodor et al. '91.

Accordingly, it is respectfully submitted that the combination of Gress et al. with Granelli-Piperno et al. and Fodor et al. '91 fails to teach, suggest, provide motivation to make, or otherwise render obvious the invention as claimed in independent Claims 38, 56 and 70. It is submitted that because the teachings of Gress et al. actually teach away from the claimed invention, there is no motivation to modify Gress et al. as suggested by the Examiner. Moreover, even if combined, which there is no motivation to do, none of the cited references either alone or in any combination teaches or suggests the step of storing in digital form each electrical output signal in a *output signal data structure*, wherein each stored digital signal is associated: "(i) with said stimulus and (ii) with the identity of said identified gene" as required by independent Claims 38, 56 and 70. Removal of this ground of rejection is respectfully requested.

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The Rejection of Claims 38,49-51, 54, 56, 63-65, 67, 70, 80-82 and 84 Under 35 U.S.C. § 103(a) As Being Unpatentable Over Gress et al., in view of Granelli-Piperno et al. in view of either Fodor et al. 1998 (US Patent No. 5,800,992) or Fodor et al., 1991 and further in view of Watson et al.

Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82 and 84 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gress et al., in view of Granelli-Piperno et al. in view of either Fodor et al. 1998 (US Patent No. 5,800,992) or Fodor et al., 1991 and further in view of Watson et al.

The Examiner characterizes the rejected claims as being drawn to assays utilizing fungal cells and cites Watson et al., pages 573-575, for its teaching that these cells contain genes that are regulated by stimuli such as metabolites.

For at least the reasons set forth in connection with the rejection of Claims 38-53, 55-66, 68-83 and 85 under 35 U.S.C. § 103(a), it is submitted that it is not obvious to combine the teachings of Gress et al., Granelli-Piperno et al., or Fodor et al., as suggested by the Examiner. This deficiency is not cured by the teachings of Watson et al. Applicants respectfully request that the rejection of 38, 49-51, 54, 56, 63-65, 67, 70, 80-82 and 84 under 35 U.S.C. § 103(a) be withdrawn.

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CONCLUSION

In view of the foregoing amendment and remarks, the application is believed to be in condition for allowance. If any issues remain that can be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone the applicants' attorney at 206.695.1655.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first-class mail with postage thereon fully prepaid and addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: June 7, 2006 Jeffrey Haubert

TJQ:TJQ

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